

WE CLAIM:

1. A method for accelerating the rate of mucociliary clearance in a subject in need of such treatment comprising administering to the subject an effective mucociliary clearance stimulatory amount of a composition comprising a Kunitz-type serine protease inhibitor and a physiologically acceptable carrier.

2. The method according to claim 1, wherein the composition is administered to the lung airways.

3. The method according to claim 1, wherein said composition is administered directly by aerosolization.

4. The method according to claim 1, wherein said composition is administered directly as an aerosol suspension into the mammal's respiratory tract.

5. The method according to claim 4, wherein said aerosol suspension includes respirable particles ranging in size from about 1 to about 10 microns.

6. The method according to claim 4, wherein said aerosol suspension includes respirable particles ranging in size from about 1 to about 5 microns.

7. The method according to claim 4, wherein said aerosol suspension is delivered to said subject by a pressure driven nebulizer.

8. The method according to claim 4, wherein said aerosol suspension is delivered to said subject by an ultrasonic nebulizer.

9. The method according to claim 4, wherein said aerosol suspension is delivered to said subject by a non-toxic propellant.

10. The method according to claim 1, wherein said carrier is a member selected from the group consisting of a physiologically buffered solution, an isotonic saline, normal saline, and combinations thereof.

11. The method according to claim 1 wherein the Kunitz-type serine protease inhibitor is aprotinin.

12. The method according to claim 1, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence:

MAQLCGL RRSRAFLALL GSLLLSGVLA -1

ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
YLTKEECLKK CATVTENATC DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150
ACMLRCFRQQ ENPPLPLGSK VVVLAGLFVM VLILFLGASM VYLIRVARRN 200
QERALRTVWS SGDDKEQLVK NTYVL 225
(SEQ ID NO.: 49).

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5  ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
   YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
   NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150
   ACMLRCFRQQ ENPPLPLGSK VVVLGAVS 179
   (SEQ ID NO.: 2),

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ADRERSIHDF	CLVSKVVGRC	RASMPRWWYN	VTDGSCQLFV	YGGCDGNSNN	50
YLTKEECLKK	CATVTENATG	DLATSRNAAD	SSVPSAPRRQ	DSEDHSSDMF	100
NYEEYCTANA	VTGPCRASRP	RWYFDVERNS	CNNFIYGGCR	GNKNSYRSEE	150
ACMLRCFRQQ	ENPPLPLGSK	VVVLAGLFVM	VLILFLGASM	VYLIRVARRN	200
QERALRTVWS	SGDDKEQLVK	NTYVL			225
(SEO ID NO.: 45).					

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ADRERSIHDF	CLVSKVVGRC	RASMPRWYIN	VTDGSCQLFV	YGGCDGNSNN	50
YLTKEECLKK	CATVTENATG	DLATSRNAAD	SSVPSAPRRQ	DSEDHSSDMF	100
NYEEYCTANA	VTGPCRASFP	RWYFDVERNS	CNNFIYGGCR	GNKNSYRSEE	150
ACMLRCFRQQ	ENPPLPLGSK	VVVLAGLFVM	VLILFLGASM	VYLIRVARRN	200
OERALRTVWS	FGD				213

25 (SEQ ID NO.: 47),

ADRERSIHDF	CLVSKVVGRG	RASMPRWWYN	VTDGSCQLFV	YGGCDGNSNN	50
YLTKEECLKK	CATVTENATG	DLATSRNAAD	SSVPSAPRRQ	DSEDHSSDMF	100
NYEEYCTANA	VTGPCRASFP	RWYFDVERNS	CNNFIYGGCR	GNKNSYRSEE	150
ACMLRCFRQQ	ENPPLPLGSK	VVVLAGLFVM	VLILFLGASM	VYLIRVARRN	200
QERALRTVWS	SGDDKEQLVK	NTYVL			225

(SEQ ID NO.: 70),

and

35

ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRO DSEDHSSDMF 100

6998

NYEEYCTANA VTGPCRASFP RWFYDVERNS CNNFIYGGCR GNKNSYRSEE 150
 ACMLRCFRQ ENPPLPLGSK VVVLAGLFVM VLILFLGASM VYLIRVARRN 200
 QERALRTVWS FGD 213
 (SEQ ID NO.: 71).

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14. The method according to claim 1, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence:

10 IHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 YLTKEECLKK CATV 64
 (SEQ ID NO.: 4),

CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 15 YLTKEECLKK C 61
 (SEQ ID NO.: 5),

YEEYCTANA VTGPCRASFP RWFYDVERNS CNNFIYGGCR GNKNSYRSEE 150
 ACMLRCFRQ 159
 20 (SEQ ID NO.: 6),

CTANAVTGPC RASFPRWYFD VERNSCNNFI YGGCRGNKNS YRSEE 150
 ACMLRC 156
 (SEQ ID NO.: 7),

25 IHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 75
 NYEEYCTANA VTGPCRASFP RWFYDVERNS CNNFIYGGCR GNKNSYRSEE 125
 ACMLRCFRQ 159

30 (SEQ ID NO.: 3),
 CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
 NYEEYCTANA VTGPCRASFP RWFYDVERNS CNNFIYGGCR GNKNSYRSEE 150
 35 ACMLRC 156
 (SEQ ID NO.: 50),

ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 25

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YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 75
NYEEYCTANA VTGPCRASFP RWFYDVERNS CNNFIYGGCR GNKNSYRSEE 125
ACMLRCFRQQ ENPPLPLGSK VVVLGAVS 179
(SEQ ID NO.: 1).

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and

ADRERSIHDF CLVSKVVGRC RASMPRWYN VTDGSCQLFV YGGCDGNSNN
50

10 YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF
100
NYEEYCTANA VTGPCRASFP RWFYDVERNS CNNFIYGGCR GNKNSYRSEE
150

ACMLRCFRQQ ENPPLPLGSK 170
(SEQ ID NO.: 52).

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15. The method according to claim 1, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence:

20 ADRERSIHDF CLVSKVVGRC RASMPRWYN VTDGSCQLFV YGGCDGNSNN 50
YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DS 92
(SEQ ID NO.: 8).

25 16. The method according to claims 12, 13, 14 or 15, wherein the Kunitz-type serine protease inhibitor is glycosylated.

17. The method according to claims 12, 13, 14 or 15, wherein the Kunitz-type serine protease inhibitor contains at least one intra-chain cysteine-cysteine disulfide bond.

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30 18. The method according to claims 12, 13, 14, or 15, wherein the Kunitz-type serine protease inhibitor contains at least one intra-chain cysteine-cysteine disulfide bond selected from the cysteine-cysteine paired groups consisting of CYS11-CYS61, CYS20-CYS44, CYS36-CYS57, CYS106-CYS156, CYS115-CYS139,
35 and CYS131-CYS152, wherein the cysteine residues are numbered according to the amino acid sequence of native human placental bikunin.

19. Use of a Kunitz-type serine protease inhibitor in manufacturing a medicament for accelerating the rate of mucociliary clearance in a subject in need of such treatment.

20. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor is in a form suitable for administration to lung airways.

21. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor is in a form suitable for administration by aerosolization.

22. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor is in a form suitable for administration as an aerosol suspension into the mammal's respiratory tract.

23. Use according to claim 22, wherein said aerosol suspension includes respirable particles ranging in size from about 1 to about 10 microns.

24. Use according to claim 22, wherein said aerosol suspension includes respirable particles ranging in size from about 1 to about 5 microns.

25. Use according to claim 22, wherein said aerosol suspension is generated by pressure driven nebulizer.

26. Use according to claim 22, wherein said aerosol suspension is generated by an ultrasonic nebulizer.

27. Use according to claim 22, wherein said aerosol suspension includes a non-toxic propellant.

28. Use according to claim 19, wherein medicament includes a carrier selected from the group consisting of a physiologically buffered solution, an isotonic saline, normal saline, and combinations thereof.

29. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor is aprotinin.

30. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence:

MAQLCGL RRSRAFLALL GSLLLLSGVLA -1

ADRSIHDF CLVSKVVGRC RASMPRWYN VTDGSCQLFV YGGCDGNSNN 50
YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150
ACMLRCFRQQ ENPPLPLGSK VVVLAGLFVM VLILFLGASM VYLIRVARRN 200
QERALRTVWS SGDDKEQLVK NTYVL 225
(SEQ ID NO.: 49).

31. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence:

AGSFLAWL GSLLLLSGVLA -1
 ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
 NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150
 5 ACMLRCFRQQ ENPPLPLGSK VVVLAVS 179
 (SEQ ID NO.: 2),

MLR AEADGVSRLG GSLLLLSGVLA -1
 ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 10 YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
 NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150
 ACMLRCFRQQ ENPPLPLGSK VVVLAVS 200
 QERALRTVWS SGDDKEQLVK NTYVL 225
 (SEQ ID NO.: 45),

MAQLCGL RRSRAFLALL GSLLLLSGVLA -1
 ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
 NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150
 20 ACMLRCFRQQ ENPPLPLGSK VVVLAVS 200
 QERALRTVWS FGD 213
 (SEQ ID NO.: 47),

ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 25 YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
 NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150
 ACMLRCFRQQ ENPPLPLGSK VVVLAVS 200
 QERALRTVWS SGDDKEQLVK NTYVL 225
 (SEQ ID NO.: 70),

and

ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
 YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100
 35 NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150
 ACMLRCFRQQ ENPPLPLGSK VVVLAVS 200
 QERALRTVWS FGD 213

(SEQ ID NO.: 71).

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~~33~~ Use according to claim 19, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence:

IHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50

YLTKEECLKK CATV 64

(SEQ ID NO.: 4),

CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50

YLTKEECLKK C 61

(SEQ ID NO.: 5),

YEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150

ACMLRCFRQ 159

(SEQ ID NO.: 6),

CTANAVTGPC RASFPRWYFD VERNSCNNFI YGGCRGNKNS YRSEE 150

ACMLRC 156

(SEQ ID NO.: 7),

IHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50

YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 75

NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 125

ACMLRCFRQ 159

(SEQ ID NO.: 3),

CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50

YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 100

NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 150

ACMLRC 156

(SEQ ID NO.: 50),

ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 25

YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DSEDHSSDMF 75

NYEEYCTANA VTGPCRASFP RWYFDVERNS CNNFIYGGCR GNKNSYRSEE 125

ACMLRCFRQQ ENPPLPLGSK VVVLGAVS 179

and

[illegible]

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34. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor comprises the amino acid sequence:

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ADRERSIHDF CLVSKVVGRC RASMPRWWYN VTDGSCQLFV YGGCDGNSNN 50
YLTKEECLKK CATVTENATG DLATSRNAAD SSVPSAPRRQ DS 92
(SEQ ID NO.: 8) .

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~~34~~
35. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor is glycosylated.

35 ~~36.~~ Use according to claim 19, wherein the Kunitz-type serine protease
25 inhibitor contains at least one intra-chain cysteine-cysteine disulfide bond.

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37. Use according to claim 19, wherein the Kunitz-type serine protease inhibitor contains at least one intra-chain cysteine-cysteine disulfide bond selected from the cysteine-cysteine paired groups consisting of CYS11-CYS61, CYS20-CYS44, CYS36-CYS57, CYS106-CYS156, CYS115-CYS139, and CYS131-CYS152, wherein the cysteine residues are numbered according to the amino acid sequence of native human placental bikunin.